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特許庁

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特許公報

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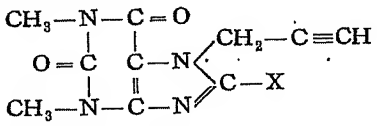
(全2頁)

7,8—置換テオフイリン誘導体の製造法

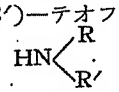
発明の詳細なる説明

本発明は7,8—置換テオフイリン誘導体の製造法に係る。

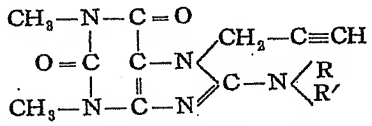
本発明は一般式



(式中Xはハロゲンを示す)の8—ハロゲノ—7プロピン(2′)—テオフイリンに一般式



(式中R、R′は、水素、脂肪族基又は芳香族基芳香脂肪族基あるいは、両者が窒素と共に閉環して異項環を形成しているものを示す)を作用させることを特徴とする一般式



(式中R、R′は前記規定と同じ)の7,8置換テオフイリン誘導体の製造法である。

本発明方法によつて得られた7,8置換テオフイリン誘導体は、何れも文献未載の新規物質であり医療上たとえば、強心利尿剤又はその合成中間体として価値のある化合物である。さらに本物質は無機酸、有機酸の塩たとえば塩酸塩、硫酸塩、硝酸塩、コハク酸塩、クエン酸塩、酒石酸塩、ピコラート、スルホナート等あるいは第四級アンモニウム塩を形成しうる。

本発明方法の原料物質として用いられる8—ハロゲノ—7プロピン(2′)テオフイリンの8位ハロゲニドとしては、クロル、ブロム、ヨード体のいずれでもよく、本物質はたとえば、8—ハロゲノテオフイリンにプロパルギルハロゲニドを作用させることにより製造される。

本発明方法は8—ハロゲノ—7プロピン(2′)テオフイリンにアンモニアまたは第1級、第2級アミンを作用させてアミノ化される。アミンとしては前記一般式$HN\begin{matrix}R\\R'\end{matrix}$のR、R′が脂肪族基、芳香族基、芳香脂肪族基あるいは、両者が窒素と共に閉環して異項環を形成している第1級、第2級アミンたとえば、メチルアミン、ジエチルアミン、アニリン、ベンチールアミン、フエニールエチルアミン、モルフオリン、ピロリジン、ピペリヂン等の中から、適宜のものが選ばれうる。これらのアミン類はさらに反応に支障なき限り、オキシ、カルボキシ、アルコキシ、カルボアルコキシあるいはこれらの置換されたアルキル基を包含していてもよい。

本発明方法は、常法に従つて脱酸剤の存在下或いは、非存在下に実施される。この際アミンの種類によつて密閉、加圧されてもよく又常温、加熱又は加熱環流下におこなつてもよい。

本反応においては、原料とするアンモニア、アミン類を過剰に使用すれば脱酸剤として作用するから特に脱酸剤を加えずに行つてもよいがアミンの塩基性が弱い場合は、一般に使用される脱酸剤たとえば、炭酸カリ、重炭酸ナトリウム、苛性カリまたはピリジン、トリエチルアミン等の反応に関与しない脱ハロゲン化水素剤を加えてもよい。さらに反応が円滑に進行し難い時は、触媒として硫酸銅、塩化銅、銅粉等を使用出来る。

反応溶媒としては、反応に支障をきたさないものなら、いずれを選択してもよく一般に原料物質を溶解するたとえばアルコール、ベンゾール、クロロホルム等が用いられる。

実施例　1

モルフオリン4.5g、8—ブロム—7プロピン(2′)テオフイリン17g、炭酸カリ4.5gをアルコール150c.c.中7時間加熱環流せしめ、後熱時濾過し、濾液のアルコールを留去し残部をアルコールより精製すれば、融点174℃の8—モルフオリノ—7プロピン(2′)テオフイリンを得る。

実施例　2

実施例1においてモルフオリンの代りにピペリヂン4.2gを用い、実施例1と同様反応処理すれば、融点183℃の8—ピペリヂノ—7プロピン(2′)テオフイリンを得る。

実施例　3

ヂエチルアミン3g、8—ブロム—7—プロピン—(2′)—テオフイリン4.5gを80c.c.のアルコールと共に耐圧びん中8時間水浴上で加熱する。後アルコールを留去し析出する結晶を含水メタノールから精製すれば融点92℃の8—ジエチルアミノ—7—プロピン—(2′)—テオフイリンをうる。

実施例　4

N—メチルピペラジン1.77g、8—ブロム—7—プロピン—(2′)—テオフイリン5g、炭酸カリ1.16gをアルコール150c.c.中7時間環流し、濾過後アルコールを留去し、残部を水より精製すれば融点146℃の8—(N—メチル—N′—ピペラヂノ)—7—プロピン—(2′)—テオフイリンをうる。

実施例　5

8—ブロム—7—プロピン(2′)—テオフイリン14g、

2—フエニールイソプロピルアミン6.4g、炭酸カリ3.4gを300c.c.のアルコール中10時間加熱する。後アルコールを留去し、残部をメタノールより精製すれば融点234～5℃の8—（2—フエニールイソプロピルアミノ）—7—プロピンテオフイリンをうる。

実施例　6

8—ブロム—7—プロピンテオフイリン7g、3—（2—エチルヘキソキシ）—プロピルアミン4.4g、炭酸カリ1.7gをアルコール150c.c.中10時間加熱する。後実施例5と同様に処理すれば融点136～7℃の8—〔3—（2—エチルヘキソキシ）—プロピルアミノ〕—7—プロピンテオフイリンをうる。

実施例　7

8—ブロム—7—プロピンテオフイリン7g、3—ジエチルアミノプロピルアミン3.1g、炭酸カリ1.7gを150c.c.のアルコール中10時間加熱する。後実施例5と同様に処理すれば融点184～5℃の8—（3—ジエチルアミノプロピルアミノ）—7—プロピンテフオリンをうる。

実施例　8

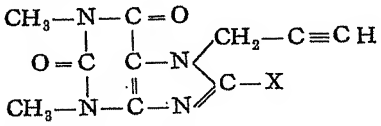
8—ブロム—7—プロピン—（2′）—テオフイリン7g、γ—〔β—（β—オキシエトオキシ）—エトオキシ〕—プロピルアミン4.6g、炭酸カリ2.15gをアルコール中実施例5と同様反応処理すれば融点151℃の8—γ—〔β—（β—オキシエトオキシ）—エトオキシ〕—プロピルアミノ—7—プロピン—（2′）—テオフイリンをうる。

実施例　9

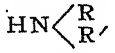
8—ブロム—7—プロピン—（2′）—テオフイリン7g、γ—モルフオリノプロピルアミン4.5g、炭酸カリ2.15gをアルコール中実施例5と同様反応処理すれば融点1.56℃の8—γ—モルフオリノプロピルアミノ—7—プロピン—（2′）—テオフイリンをうる。

特許請求の範囲

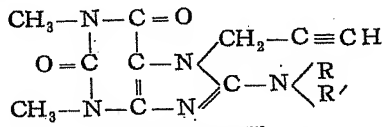
一般式



（式中Xはハロゲンを示す）の8—ハロゲノ—7プロピン（2′）—テオフイリンに一般式



（式中R、R′は、水素、脂肪族基または芳香族基、芳香脂肪族基あるいは両者が窒素と共に閉環して異項環を形成しているものを示す）を作用させることを特徴とする一般式



（式中R、R′は前記規定と同じ）の7,8置換テオフイリン誘導体の製造法。

PTO 2003-5084
S.T.I.C. Translations Branch

PTO: 2003-5084

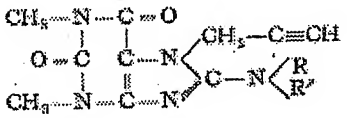
Japanese Published Examined Patent Application (Kokoku Koho) No. S37-4895, Patented Date: June 16, 1962; Application No. not listed; Application Date: August 18, 1959; Inventor: Michio Nakanishi; Applicant: Yoshitomi Pharmaceutical Corporation; Japanese Title: 7,8-Chikan Teofirin Yuudoutai no Seizou Houhou (Method for Production of 7,8-Substituted Theophylline Derivatives)

Method for Production of 7,8-Substituted Theophylline Derivatives

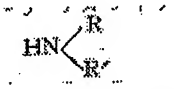
Detailed Description of the Invention

This invention pertains to a producing method for 7,8-substituted theophylline derivatives.

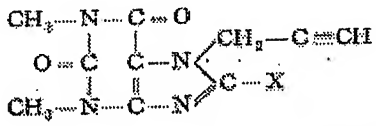
The invention is a method for production of 7,8-substituted theophylline derivatives as indicated by the following general formula:



(In the formula, R and R' represent hydrogen, an aliphatic group, aromatic group, aroma-aliphatic group or both aliphatic and aromatic groups with a different top ring formed by closing the ring with nitrogen), characterized in that



(In the drawing, R and R' indicate the same components as disclosed above) is reacted to 8-halogeno-7propyne (2')-theophylline as indicated by the following formula:

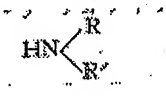


(In the formula, X represents halogen).

All of the 7,8-substituted theophylline derivatives obtained by the method of the invention are new substances as not listed in any references. In the medical field, the

derivatives are valuable compounds as cardiotonic diuretics or the synthetic intermediate substances. These substances can form inorganic acid and organic acid salts. For example, the following types of the salts are formed: hydrochloride; sulfate; nitrate; succinate; citrate; tartrate; picolate; sulfonate; a quaternary ammonium salt.

Any type from chlor, bromine or iodine is used as the 8th halogenide of 8-halogeno-7 propyne (2') theophylline that is used as a raw substance for the method of the invention. This substance is produced by a reaction between propargyl halogenide and 8-halogeno theophylline.

According to the method of the invention, 8-halogeno-7 propyne (2') theophylline is aminated by reacting ammonium or primary amine and secondary amine to it. As for these amines, the following types of primary and secondary amines wherein R and R' of the aforementioned general formula  represent an aliphatic, aromatic group, aroma-aliphatic group or both aliphatic and aromatic groups with a different top ring formed by closing the ring with nitrogen are selected as needed as long as the reaction does not develop any problems: methyl amine; diethyl amine; aniline; pentyl amine; phenylethyl amine; morpholine; pyrrolidine; piperidine. These amines can further contain an oxy group, a carboxy group, an alkoxy group, a carboalkoxy group or an alkyl group formed by these groups substituted.

The method of the invention is carried out under the presence or absence of a deoxidizer by using a conventional method. At this time, a sealing or pressurizing means can be applied depending on the types of amines. Or the method can be used at a normal temperature, a high temperature or at a reflux by heating.

In this reaction, if ammonia and amines as crude substances are excessively used, they act as deoxidizers. Because of this effect, no regular deoxidizers are required. When the base property of amines is low, conventionally used deoxidizers, for example, dehalogenized hydrogen agents that do not involve in the reaction can be added, such as potassium carbonate, sodium bicarbonate, caustic potassium, pyridine and triethyl amine. If the reaction does not smoothly progress, copper sulfate, copper chloride and a copper powder are used as catalysts.

As for reaction solvents, any solvents can be selected as long as the reaction does not develop any problems. Solvents that dissolve the crude substances are usually used: alcohol; benzole; chloroform.

Embodiment 1

The following substances at the following amounts are circulated in alcohol at 150 c.c. for 7 hours by a heating means: morpholine at 4.5g; 8-bromine-7 propyne (2') theophylline at 17g; potassium carbonate at 4.5g. After the heating, the solution is filtered. When the alcohol in the filtered solution is distilled and when the remaining portion is purified from alcohol, 8-morpholino-7 propyne (2') theophylline at a 174°C melting point is obtained.

Embodiment 2

Piperidine at 4.2g is used in lieu of morpholine as in Embodiment 1. When a reaction process is applied as similar to as in Embodiment 1, 8-piperidino-7 propyne (2') theophylline at a 183°C melting point is obtained.

Embodiment 3

Diethyl amine at 3g and 8-bromine-7-propyne-(2')-theophylline at 4.5g are supplied in a pressure resistant bottle with alcohol at 80 c.c. The solution is then heated in the water bath for 8 hours. After this, alcohol is distilled. When the deposited crystal is purified from water containing methanol, 8-diethyl amino-7-propyne-(2')-theophylline at a 92°C melting point is obtained.

Embodiment 4

The following substances at the following amounts are circulated in alcohol at 150 c.c. for 7 hours: N-methyl piperadine at 1.77g; 8-buromine-7-propyne-(2')-theophylline at 5g; potassium carbonate at 1.16g. After the solution has been filtered, alcohol is distilled. When the remaining portion is purified from water, 8-(N-methyl-N'-piperadino)-7-propyne-(2')-theophylline at a 146°C melting point is obtained.

Embodiment 5

The following substances at the following amounts are heated in alcohol at 300 c.c. for 10 hours: 8-bromine-7-propyne (2')-theophylline at 14g; 2-phenyl isopropyl amine at 6.4g; potassium carbonate at 3.4g. After this, alcohol is distilled. When the remaining portion is purified from methanol, 8-(2-phenyl isopropyl amino)-7-propyne theophylline at a 234 to 235°C melting point is obtained.

Embodiment 6

The following substances at the following amounts are heated in alcohol at 150 c.c. for 10 hours: 8-bromine-7-propyne theophylline at 7g; 3-(2-ethyl hexoxy)-propyl amine at 4.4g; potassium carbonate at 1.7g. After this, when a process as similar to as in Embodiment 5 is applied, 8-[3-(ethyl hexoxy)-propyl amino]-7-propyne theophylline at a 136 to 137°C melting point is obtained.

Embodiment 7

The following substances at the following amounts are heated in alcohol at 150 c.c. for 10 hours: 8-bromine-7-propyne theophylline at 7g; 3-diethyl amino propyl amine at 3.1g; potassium carbonate at 1.7g. After this, when a process as similar to as in Embodiment 5 is applied, 8-(3-diethyl amino propyl amino)-7-propyne theophylline at a 184 to 185°C melting point is obtained.

Embodiment 8

The following substances at the following amounts are mixed in alcohol: 8-bromine-7-propyne-(2')-theophylline at 7g; γ-[β-(β-oxyethoxy)-ethoxy]-propyl amine at 4.6g; potassium carbonate at 2.15g. When a reaction process is applied as similar to as in Embodiment 5, 8-γ-[β-(β-oxyethoxy)-ethoxy]-propyl amino-7-propyne-(2')-theophylline at a 151°C melting point is obtained.

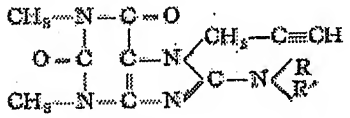
Embodiment 9

The following substances at the following amounts are mixed in alcohol: 8-bromine-7-propyne-(2')-theophylline at 7g; γ-morpholino propyl amine at 4.5g; potassium

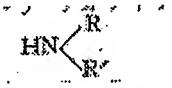
carbonate at 2.15g. When a reaction process is applied as similar to as in Embodiment 5, 8-γ-morpholino propyl amino-7-propyne-(2')-theophylline at a 1.56°C melting point is obtained.

Claim

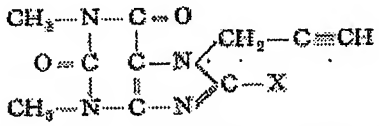
The invention is a method for production of 7,8-substituted theophylline derivatives as indicated by the following general formula:



(In the formula, R and R' represent hydrogen, an aliphatic group, aromatic group, aroma-aliphatic group or both aliphatic and aromatic groups with a different top ring formed by closing the ring with nitrogen), characterized in that



(In the drawing, R and R' indicate the same components as disclosed above) is reacted to 8-halogeno-7propyne (2')-theophylline as indicated by the following formula:



(In the formula, X represents halogen).

U.S. Patent and Trademark Office
Translations Branch
8/27/03
Chisato Morohashi

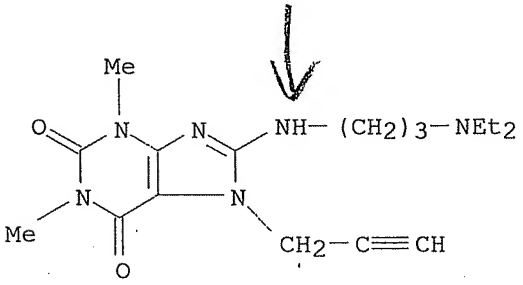
L23 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2002 ACS
1963:409047 Document No. 59:9047 Original Reference No. 59:1658f-g
7,8-Substituted theophyllines. Nakanishi, Michio (Yoshitomi Pharmaceutical Industries, Ltd.). JP 37004895 19620616 Showa, 2 pp. (Unavailable). APPLICATION: JP 19590818.

AB A mixt. of 4.5 g. morpholine, 17 g. 8-bromo-7-propyn-2-yltheophylline, 4.5 g. K2CO3, and 150 cc. EtOH is refluxed for 7 hrs. to give 8-morpholino-7-propyn-2-yltheophylline, m. 174.degree. (EtOH). Similarly prepd. are the following 7-propyro-2-yl-7-(R-substituted) theophyllines. (R and m.p. given): piperidino, 183.degree.; Et2N, 92.degree.; N-methyl-N'-piperazino, 146.degree.; 2-phenylisopropylamino, 234-5.degree.; 3-(2-ethylhexyloxy)propylamino, 136-7.degree.; 3-diethylaminopropylamino, 184-5.degree.; .gamma.-[.beta.-(.beta.-hydroxyethoxy)ethoxy]propylamino, 151.degree.; .gamma.-morpholinopropylamino, 156.degree.. The compds. are useful as diuretics and cardiotonics.

IT **98147-52-5**, Theophylline, 8-[[3-(diethylamino)propyl]amino]-7-(2-propynyl)-
(prepn. of)

RN 98147-52-5 HCAPLUS

CN Theophylline, 8-[[3-(diethylamino)propyl]amino]-7-(2-propynyl)- (7CI) (CA INDEX NAME)



L23 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2002 ACS
1963:33375 Document No. 58:33375 Original Reference No. 58:5670g-h,5671a-e
Caffeine-8-alkylene diamines. Klosa, Josef (Privat-Lab., Berlin Zehlendorf, Germany). J. Prakt. Chem., 18, 97-106 (Unavailable) 1962.

AB The title compds. were prepd. by reaction of 8-chloro- or 8-bromocaffeine (I or II) and alkylenediamines or by treatment of 8-(.beta.-chloroalkyl)alkylamino- or aminocaffeine with primary or secondary bases. 8-(.beta.-Hydroxyethyl)aminocaffeine (10 g.) was added in portions to 10 ml. SOCl2, the mixt. heated 20-30 min. on a steam bath, and washed many times with refluxing C6H6 to give 11 g. 8-(.beta.-chloroethyl)aminocaffeine (III), m. 225-7.degree. (MeOH). Similarly, 50 g. 8-(.gamma.-hydroxypropyl)amino-caffeine and 100 ml. SOCl2. gave 55 g. 8-(.beta.-chloropropyl)aminocaffeine (IV), m. 210-12.degree. (EtOH), and 40 g. 8-(.beta.-hydroxyethyl)-methylaminocaffeine and 40 ml. SOCl2 refluxed 2 hrs. and then n2poured onto ice and neutralized with dil. NH3 gave 8-(.beta.-chloroethyl)methylaminocaffeine (V). I (22 g.) and 23 g. Et2NCH2-CH2NH2 were rubbed together, heated to 140.degree. to effect soln., and then refluxed 20 min. at 150-70.degree.. The mixt. was cooled, dissolved in hot EtOH, cooled, and filtered and the crystals dissolved in EtOH, treated with HCl-EtOH, and then with double the vol. of Et2O to give 80% N,N-diethyl-N'-(caffein-8-yl)ethylenediamine hydrochloride, m. 288-90.degree.; free base m. 186-8.degree. (C6H6-petr. ether); methobromide m. 230.degree.. I (44 g.) and 42 ml. Et2N(CH2)3NH2 heated a few min. at 160-70.degree. gave a mixt. which soon solidified and was